

Application of the HFA-PEFF algorithm to characterize and score cardiac abnormalities in women with preeclampsia

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Objective: Preeclampsia imposes significant cardiovascular stress and frequently diastolic dysfunction. New recommendations advise multimodal assessments of cardiac function. The Heart Failure Association – Pretest assessment, Echocardiography and Functional testing, and Final etiology (HFA-PEFF) scoring system integrates echocardiographic indices and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and provides a structured way to characterize cardiac function. This study applied the HFA-PEFF algorithm to assess cardiac function in preeclampsia and its association with maternal and fetal outcomes.

Methods: This prospective observational study was conducted between 2019 and 2022. Ninety women with preeclampsia and 46 normotensive controls were assessed using echocardiography and NT-proBNP levels according to the HFA-PEFF scoring system. Patients were categorized into high (≥ 5 points), intermediate (2–4 points), or low (0–1 points) score groups. Maternal and fetal outcomes were recorded.

Results: Women with preeclampsia were more frequent in the high (27 vs. 0%) and intermediate (56 vs. 28%) score groups and less frequent in the low-score group (18 vs. 72%, $P < 0.001$) compared to controls. The median HFA-PEFF score was 3 points [interquartile range (IQR) 2–5] in women with preeclampsia and 1 point (IQR 0–2) in controls ($P < 0.001$). The HFA-PEFF score groups did not relate to core outcomes overall but small-for-gestational age neonates and higher soluble fms-like tyrosine kinase-1/placental growth factor ratio (sFLT/PIGF) ratios were more common in the HFA-PEFF high-score group ($P = 0.011$, $P = 0.036$).

Conclusion: The HFA-PEFF algorithm effectively detected cardiac dysfunction – reflected in structural changes, functional impairment, and elevated heart failure biomarkers – in women with preeclampsia. NT-proBNP may serve as potential screening tool for HFA-PEFF score.

Keywords: diastolic dysfunction, echocardiography, HFA-PEFF, heart failure with preserved ejection fraction, hypertension, N-terminal pro-B-type natriuretic peptide, preeclampsia, pregnancy complications, sFLT/PIGF ratio, small-for-gestational-age

Abbreviations: bpm, beats per minute; HFA-PEFF, Heart Failure Association of the European Society of Cardiology: Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology; HFpEF, Heart failure with preserved Ejection Fraction; LAVI, Left Atrium Volume Index; LV GLS, Left Ventricular Global Longitudinal strain; LVMI, Left Ventricle Mass Index; LVWT, Left Ventricular Wall Thickness; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RWT, Relative Wall Thickness; sFlt-1/PIGF, soluble fms-like tyrosine kinase-1/placental growth factor ratio; SGA, Small-for-gestational-age; TR maxPG, Tricuspid maximal regurgitation pressure gradient

INTRODUCTION

Preeclampsia affects 3–5% of pregnancies and remains a leading cause of maternal morbidity and mortality [1,2]. The cause of preeclampsia is not fully understood. A widely accepted theory suggests that placental malperfusion triggers a systemic vascular inflammation cascade [1]. Preeclampsia is clinically defined as hypertension accompanied by signs of organ dysfunction, occurring after 20 weeks of gestation [3]. Women with preeclampsia have a two to three times increased risk of cardiovascular disease and heart failure with preserved ejection fraction (HFpEF) later in life [4–6]. Several studies have investigated the impact of preeclampsia on the cardiovascular system, consistently reporting preserved left

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ventricular (LV) ejection fraction, but evidence of impaired diastolic function [6–7]. Impaired diastolic function may contribute to elevated pulmonary vascular pressures and pulmonary edema, which are severe complications of preeclampsia [8,9]. Echocardiographic studies have identified alterations in key diastolic function parameters such as relaxation time (e') and estimated filling pressures (E/e') [7]. However, most studies have focused on individual parameters rather than employing an integrated assessment [10]. Given the complexity of diastolic dysfunction, a multimodal approach is recommended [11–13]. The HFA-PEFF algorithm, developed by the Heart Failure Association of the European Society of Cardiology, provides a structured framework for evaluating diastolic function and HFpEF. This algorithm incorporates and grades several different echocardiographic indices depicting the functional and morphological aspects of the heart in combination with levels of the serum biomarker for heart failure and cardiac load, NT-proBNP [14]. While originally intended to assess the risk of HFpEF, it provides a structured approach to summarizing and characterizing cardiac abnormalities and may be a useful tool in the context of preeclampsia.

The primary aim of this study was to assess the applicability of the HFA-PEFF algorithm in preeclampsia to characterize cardiac abnormalities and compare them with cardiac function in normotensive pregnant women. The secondary aim was to assess whether higher scores were associated with a more complex disease, as measured by a set of maternal and fetal core outcomes.

METHODS

Ethics and registration

This study was approved by the Regional Research Committee in Gothenburg (approval numbers 2019-03734 and 2020-02291). Written informed consent was obtained from all participants prior to enrollment. This study was part of the Gothenburg Preeclampsia Adverse Event (GoPROVE) biobank and database (ISRCTN13060768) [15].

Study population and settings

Sahlgrenska University Hospital/Östra, Gothenburg, Sweden, is a tertiary university hospital with approximately 10 000 births annually. All pregnant women were eligible for inclusion between May 2019 and February 2022. Women were recruited into two groups: normotensive controls and women diagnosed with preeclampsia. The inclusion criteria for normotensive controls were normal pregnancy after 20 weeks of gestation. Preeclampsia was defined by new-onset hypertension ($\geq 140/90$ mmHg) after 20 weeks of gestation with one or more end-organ complications. Furthermore, for inclusion in the study, verified excessive proteinuria (albumin/creatinine ratio >8 mg/mmol) was needed. Maternal and fetal core outcomes were defined according to the consensus document published by the International Collaboration to Harmonize Outcomes for preeclampsia (iHOPE) [16]. Exclusion criteria for normotensive controls and women with preeclampsia included multifetal pregnancies and any significant preconceptional systemic diseases, such as heart disease, hypertension,

diabetes, or renal failure. The women were enrolled by trained staff, including PhD students and research assistants.

Data collection

Demographics, medical history, pregnancy data, complications, and standard laboratory results were included in the GoPROVE database, an electronic case report form (eCRF) with double authentication provided by Omda (MedSciNet) [15]. Data was collected on admission using questionnaires and interviews. Maternal and fetal core outcomes and standard laboratory results were collected from medical records and charts.

In addition, NT-proBNP was analyzed, and echocardiographic assessments were performed. NT-proBNP was analyzed within 24 h of the echocardiographic examination. Blood samples were collected in 5 ml lithium-heparin gel tubes, centrifuged, and plasma was analyzed for NT-proBNP levels at the accredited hospital laboratory at Sahlgrenska University Hospital, Gothenburg, using the Alinity I platform (Abbott, Austin, Texas, USA), an immunochemical two-step BNP assay.

Samples for sFlt-1 and PlGF analysis were collected with a fresh venipuncture, in serum tubes without gel, at inclusion. The samples were centrifuged at 2000g for less than 24 h of sampling and aliquoted and stored at -80°C in Biobank Väst, an in-hospital biobank. The samples were analyzed with the automatized platform Delfia Xpress 1-2-3 (Perkin-Elmer, Waltham, USA) at iLab Medical AB, Gothenburg, Sweden.

Echocardiographic protocol

Comprehensive echocardiographic assessments were performed by experienced echo technicians after enrollment but before delivery, using the E95 system (General Electric, Fairfield, Connecticut, USA). Echocardiography was performed only during office hours and on days when the study operators were available. Offline analysis was conducted by one of the technicians using EchoPAC version 204 (General Electric) in accordance with published guidelines, blinded to the groups. Left ventricular (LV) mass index (LVMI) was calculated using linear measurements and indexed to body surface area (BSA). Volumes were measured using the modified Simpson method, and LV ejection fraction (LVEF) was calculated. Left atrial volume was measured in apical two-chamber and four-chamber views at end-systole and indexed to BSA [17]. Stroke volume in the LV outflow tract was determined using pulsed-wave Doppler. Tissue Doppler was recorded at the septal and lateral mitral annulus, and early diastolic velocities (e') were measured. The E/e' ratio was calculated using the average of the septal and lateral e' velocities. The tricuspid regurgitation velocity was measured in a modified apical four-chamber view using continuous wave Doppler. LV global longitudinal strain (GLS) was analyzed using speckle-tracking echocardiography in apical long-axis, four-chamber, and two-chamber views, and absolute values were reported [18]. Reproducibility was tested in 24 randomly selected patients and was estimated using intraclass correlation coefficients. Intraobserver (interobserver)

variability was for e' septal 0.98 (0.99), e' lateral 0.97 (0.98), E/e' mean 0.97 (0.98), LAVI 0.87 (0.92), and GLS 0.91 (0.82).

The HFA-PEFF algorithm, scoring and categorization

The HFA-PEFF algorithm was used to define cardiac function in women with preeclampsia and controls [14]. The HFA-PEFF algorithm is based on three domains, each scored from 0 to 2 points. The domains are cardiac function, by echocardiographic parameters e' , E/e' , TR V_{\max} , and GLS, cardiac morphology by echocardiographic measurements of LAVI, LV MI, RWT, and LVWT, and NT-proBNP levels. [14]. All women were classified into a high-score group (5–6 points), an intermediate-score group (2–4 points), or a low-score group (0–1 points). Supplement Table 1, <http://links.lww.com/HJH/C872>.

Outcomes

The primary outcome was the distribution of HFA-PEFF score groups across women with preeclampsia and controls. The secondary outcome was the prevalence of maternal and fetal core outcomes across the HFA-PEFF score groups in women with preeclampsia [16].

Statistics

Normally distributed continuous data is presented as mean \pm standard deviation, whereas non-normally distributed data is reported as medians with interquartile ranges. To compare continuous variables between the two groups, the Student's t -test was used for normally distributed data, and the Mann–Whitney U test was applied for non-normally distributed data. Fisher's exact test was used to compare binary outcomes, while the chi-squared (χ^2) test was used to analyze nominal variables with more than two categories. The Mantel-Haenszel test was used to analyze trends in categorical variables (primary and secondary aims), while the Jonckheere-Terpstra test was applied to continuous data across the three different HFA-PEFF score groups: the high-score group, the intermediate-score group, and the low-score group.

We used ordinal logistic regression (cumulative logit, proportional odds) with the HFA-PEFF score as the ordered outcome. Results are presented as common odds ratios (cOR). The proportional-odds assumption was assessed using the Test of Parallel Lines.

The null hypothesis was rejected for values of $P < 0.05$.

We aimed to include at least 20 women with cardiac abnormalities to allow adequate characterization and to assess associations with core maternal and fetal outcomes [16]. A predefined interim analysis after inclusion of 20 patients showed that 25% met at least one criterion for diastolic dysfunction. Therefore, the target sample size was adjusted to include at least 80 women with preeclampsia. Given the expected lower score and less variability in scores in the control group, a 2:1 inclusion ratio was adopted.

Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the SPSS software (version 25.0; Armonk, New York, USA).

RESULTS

Three hundred and fifty-two women with preeclampsia were included in the GoPROVE project between May 2019 and February 2022. Of the 352 women, all eligible women (not in labor) were asked to undergo echocardiography (available at 08:00–16:00, Monday to Friday), and 103 were included in this study. Twelve women were later excluded because of incomplete testing or lack of significant proteinuria and one due to missing NT-proBNP sample, leaving 90 women with preeclampsia in the study. During this period, 114 normotensive controls were included in the GoPROVE project, of which 54 were enrolled, and seven were excluded because they developed hypertension or preeclampsia after inclusion and one for missing NT-proBNP sample, leaving 46 normotensive controls (Fig. 1).

Baseline characteristics

Women with preeclampsia were more frequently nulliparous than were normotensive controls. There was no difference in maternal age or BMI between the groups. None of the women in either group smoked. The median gestational age at echocardiography was higher in women with preeclampsia (35+3 weeks) than in normotensive controls (31+6 weeks) ($P = 0.015$). The median gestational age at delivery was 35+5 weeks in the preeclampsia group and 40+3 weeks in the normotensive control group ($P < 0.001$). Ninety-three percent of women with preeclampsia had received at least one type of antihypertensive treatment within 24 h of echocardiography. A trend was observed towards a higher prevalence of asthma in women with preeclampsia (9 vs. 0%, $P = 0.051$) (Table 1). All included women were in sinus rhythm.

Echocardiographic parameters in women with preeclampsia vs. normotensive controls

Details of echocardiographic measurements and HFA-PEFF scoring criteria are presented in Table 2. There was no difference in ejection fraction or LV GLS between the groups. With respect to functional measurements, both septal and lateral e' were significantly lower in women with preeclampsia than in normotensive controls. (8.5 vs. 10.5 cm/s, $P < 0.001$ and 11.7 vs. 14.6 cm/s, $P < 0.001$, respectively). In total, 32 women with preeclampsia (36%) had a lower septal e' (< 7 cm/s) or lateral e' (< 10 cm/s), compared to four normotensive controls (9%, $P < 0.001$). TR V_{\max} was higher in women with preeclampsia (2.18 m/s) than in normotensive controls (1.87 m/s, $P = 0.003$), although measurable tricuspid regurgitation was present in approximately 25% of the population, and no women had a TR V_{\max} greater than 2.8 m/s. An E/e' ratio, at least 15 was not observed in any woman, while 28% of the women in the preeclampsia group scored in the E/e' range of 9–14.

Regarding morphological measurements, LAVI was higher in women with preeclampsia (31.4 vs. 28.2 ml, $P = 0.009$), and a LAVI greater than 34 ml was more common in the preeclampsia group compared to normotensive controls (39 vs. 13%, $P = 0.005$). The LVMI was also higher in women with preeclampsia (77 vs. 68 g/m², $P = 0.003$). Furthermore, both RWT and LVMI were higher in women with preeclampsia, but in total only in 7 women (8%).

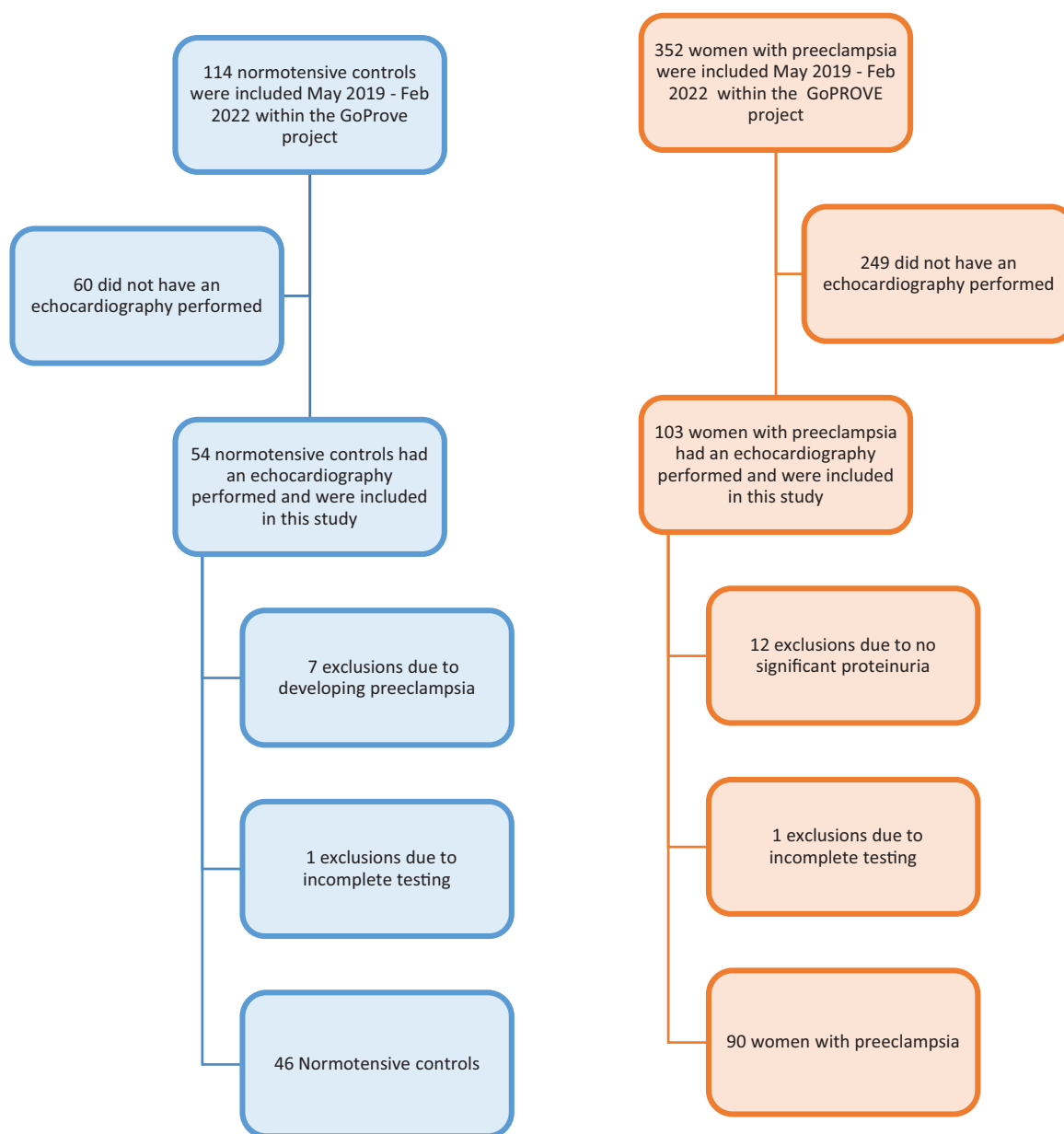


FIGURE 1 Study flow chart.

HFA-PEFF score and categorization in women with preeclampsia vs. normotensive controls

Women with preeclampsia had a median HFA-PEFF score of 3 points [interquartile range (IQR) 2–5] compared to a score of 1 point (IQR 0–2), $P < 0.001$, in normotensive controls (Table 2).

In the preeclampsia group, 24 women (27%) were classified into the high-score group (HFA-PEFF score ≥ 5), compared to none (0%) in the normotensive control group ($P > 0.001$). Furthermore, women with preeclampsia were more frequent in the intermediate-score group (HFA-PEFF score 2–4 points, 56 vs. 28%), and less commonly in the low-score group compared to normotensive controls (HFA-PEFF score 0–1 points, 18 vs. 72%, $P > 0.001$) (Table 2). The Mantel–Haenszel test

for trend showed a significant difference in the distribution of score categories between the groups ($P < 0.001$) (Fig. 2).

N-terminal pro-B-type natriuretic peptide in women with preeclampsia vs. normotensive controls

The median serum NT-proBNP concentration was higher in women with preeclampsia [235 ng/l (IQR 114–485)] than in normotensive controls [36 ng/l (IQR 21–74)], $P < 0.001$, Table 2. Women with preeclampsia more frequently had NT-proBNP levels of 125–20 ng/l (17 vs. 11%) or greater than 220 ng/l (52 vs. 4%), compared to normotensive controls ($P < 0.001$), generating an HFA-PEFF score of 1 and 2 points, respectively.

TABLE 1. Baseline data for women with preeclampsia and normotensive controls

		Women with preeclampsia (n=90)	Normotensive controls (n=46)	P value
Demographic	Age at inclusion, years	30 (28–34)	32 (30–34)	0.169
	BMI before pregnancy (kg/m ²)	25 (23–30)	24 (22–28)	0.081
Ethnicity	Caucasian	80 (89)	46 (100)	
	African	4 (4)	0 (0)	
	Asian	6 (7)	0 (0)	
Use of drugs	Cigarette smoker	0 (0)	0 (0)	–
	Use of snuff	0 (0)	1 (2)	0.338
	Use of alcohol	0 (0)	0 (0)	–
Medical history	Nulliparous	79 (88)	26 (57)	<0.001
	Rheumatoid arthritis	1 (1)	0 (0)	1
	Venous thromboembolism	1 (1)	0 (0)	1
	Asthma	8 (9)	0 (0)	0.051
	Migraine	7 (8)	1 (2)	0.263
	Anxiety disorder	3 (3)	0 (0)	0.551
Use of medications	Levothyroxine	4 (4)	2 (4)	1
	ASA	6 (7)	1 (2)	0.422
	LMWH	8 (9)	1 (2)	0.164
Gestational age	At diagnosis, weeks + days	34+0 (31+0–36+5)	–	–
	at time of echocardiography (weeks + days)	34+6 (32+1–37+1)	31+6 (26+6–36+2)	0.015
	At delivery (weeks + days)	35+5 (33+1–37+4)	40+3 (39+2–41+0)	<.001

Values are presented as n (%), median, interquartile range. mean±SD, Mann–Whitney U test, Students t test. A P value <0.05 is considered significant. ASA, acetylsalicylic acid. LMWH, low-molecular-weight heparin.

Baseline data, sFlt/PlGF ratio and maternal and fetal core outcomes of preeclampsia in the HFA-PEFF groups, in women with preeclampsia

Data are presented in Table 3. There were no differences in age, BMI, gestational age at diagnosis or echocardiography, or blood pressure between the three HFA-PEFF groups. In total, 75 women with preeclampsia (82%) had at least one maternal or fetal core outcome. Preterm birth (<37 weeks) was most common, occurring in 63% (n=57) of women with preeclampsia (Table 3). The distribution of complications did not differ across the HFA-PEFF scoring categories, being present in 88% of those with normal cardiac function, and in 80 and 88% of those in the intermediate-score or high-score groups, respectively (P=0.887). Women with at least one maternal or fetal core outcome did not have higher HFA-PEFF scores. Small-for-gestational age was associated with a higher classification in the HFA-PEFF system, being present in 19% of those in the low-score group, 24% of those with an intermediate score, and 54% of those with a high HFA-PEFF score (P=0.011). A higher sFLT/PlGF ratio was related to a higher HFA-PEFF score (P=0.036).

In an ordinal logistic regression analysis, a higher SBP at inclusion, a small-for-gestational age infant, and a higher sFLT/PlGF ratio were correlated with higher HFA-PEFF scores (P=0.046, P=0.005, P=0.010). In multivariate analysis, only SGA remained correlated to a higher HFA-PEFF score (P=0.009), (supplements, Table 3, <http://links.lww.com/HJH/C872>).

DISCUSSION

When applying the HFA-PEFF algorithm to 90 women with preeclampsia, 27% had a high score (≥5 points), despite early detection were likely as all women in the study were

included in the national maternity care program, and 93% had received antihypertensive treatment at time of investigation, which reflects the clinical situation in Sweden well and we believe enhances external validity. Among the 46 normotensive controls, none had a high score. Higher scores were not associated with a more complex disease, but higher sFlt/PlGF ratios and small-for-gestational age neonates were more common in the higher score groups, of which only small-for-gestational age could be confirmed in a multivariable regression analysis (Table 3, Supplement Table 3, <http://links.lww.com/HJH/C872>).

Similar to several previous studies, the systolic parameter ejection fraction and cardiac output were not affected in women with preeclampsia compared to normotensive controls [10]. However, all three domains of the HFA-PEFF algorithm, functional, morphological, and biomarker of cardiac load (NT-proBNP), detected pathology in women with preeclampsia. In the functional domain, measuring myocardial relaxation capacity and its relationship to flow in the rapid flow phase of diastole (e'lat, e'sep, and E/e'), when comparing women with preeclampsia and normotensive controls, suggest an impact outside of pregnancy alone. Women with preeclampsia had higher tricuspid regurgitation velocities, but none of the women had a velocity-fulfilling HFA-PEFF criteria (>2.8m/s).

All morphological indices were higher in the preeclampsia group than in the control group. LAVI contributed the most to scoring, affecting over half of the women with preeclampsia and one-third of the controls. While mild left atrial enlargement may reflect physiological adaptations to pregnancy, a more pronounced increase in preeclampsia likely indicates elevated afterload, volume overload, or diastolic dysfunction [14]. The other morphological parameters (LWMI, LVWT, and RWT) were higher in the preeclampsia group, but only a few of the participants had

TABLE 2. HFA-PEFF score, NT-proBNP, echocardiographic data, blood pressures, and treatment in women with preeclampsia and normotensive controls, at examination

Category	Variable	Women with preeclampsia (n=90)	Normotensive controls (n=46)	P value	
HFA-PEFF score	Total score (points)	3 (2–5)	1 (0–2)	<0.001	
	Low score (0–1 point)	16 (18)	33 (72)		
	Intermediate score (2–4 points)	50 (56)	13 (28)		
	High score (5 points or more)	24 (27)	0 (0)		
NT-proBNP	NT-proBNP (ng/l)	235 (114–485)	36 (21–74)	<0.001	
	<125 ng/l	28 (31)	39 (85)		
	125–220 ng/l	15 (17)	5 (11)		
	>220 ng/l	47 (52)	2 (4)		
Echocardiographic data	Ejection fraction (%)	61 ± 5	60 ± 5	0.056	
	Stroke volume (ml)	84 ± 17	78 ± 16	0.085	
	Heart rate (bpm)	76 ± 11	76 ± 11	0.721	
	Functional	LV GLS (%)	18.5 ± 2	18.9 ± 1.9	0.398
		e' septal (cm/s)	8.5 ± 1.8	10.5 ± 2.3	<0.001
		e' lateral (cm/s)	11.7 ± 2.6	14.6 ± 2.6	<0.001
	E/e'	7.98 (6.67–9.36)	5.68 (4.88–6.52)	<0.001	
	TR present [n (%)] ^a	20 (22)	13 (28)	0.529	
	TR V _{max} (m/s)	2.18 (2.00–2.50)	1.87 (1.80–1.94)	0.003	
	Morphological	LAVI (ml/m ²)	31.4 ± 6.4	28.2 ± 6.0	0.009
LVMI (g/m ²)		77 (67–86)	68 (62–77)	0.003	
	RWT	0.31 (0.28–0.33)	0.29 (0.26–0.31)	0.007	
	LVWT (mm)	10.3 (9.1–10.9)	8.9 (8.2–9.5)	<0.001	
Categorical	e' septal <7 or e' lateral <10	32 (36)	4 (9)	<0.001	
	E/e' <9	62 (69)	44 (96)	<0.001	
	9–14	25 (28)	2 (4)		
	≥15 [n (%)]	0 (0)	0 (0)		
	TR V _{max} >2.8 m/s	0 (0)	0 (0)		
	LV GLS <16%	6 (7)	3 (7)	0.71	
	LAVI <29 (ml/m ²)	38 (42)	26 (57)	0.005	
	29–34	16 (18)	8 (17)		
	>34	35 (39)	6 (13)		
	LVMI <95 g/m ²	81 (90)	45 (98)	0.097	
	95–122	8 (9)	1 (2)		
	≥122	1 (1)	0 (0)		
	RWT >0.42	2 (2)	0 (0)	0.548	
	LVWT >12 mm	5 (6)	1 (2)	0.664	
Blood pressure	SBP (mmHg)	146 ± 13	117 ± 10	<0.001	
	DBP (mmHg)	91 ± 10	73 ± 7	<0.001	
Treatment	Any hypertensive treatment <24h before echocardiography	84 (93)	0 (0)	<0.001	

Values are presented as n (%), median, interquartile range, mean ± SD, Mann–Whitney U test, Students t test. A P value <0.05 is considered significant. bpm, beats per minute; LAVI, left atrium volume index; LV GLS, left ventricular global longitudinal strain; LVMI, left ventricle mass index; LVWT, left ventricular wall thickness; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RWT, relative wall thickness; TR maxPG, tricuspid maximal regurgitation pressure gradient.

^aOnly women with a measurable tricuspid regurgitation.

abnormal values, which may be due to the short duration of disease. Regarding NT-proBNP, a serum biomarker of wall stress and elevated pressures, the HFA-PEFF algorithm clearly reflected the difference between the groups in this study (235 vs. 36 ng/l, $P=0.001$). As there were no cases of atrial fibrillation or long-term hypertensive disease, both of which affect NT-proBNP levels, it is likely a reliable marker of increased cardiac stress in women with preeclampsia.

Studies have shown an elevated risk of HFpEF later in life in women with preeclampsia during pregnancy [5]. The fact that some women with preeclampsia have diastolic dysfunction or even HFpEF during pregnancy does not mean that the diagnosis is chronic but is likely, at least in part, reversible. Melchiorre *et al.* [19] showed that healthy pregnant women show signs of maladaptation of heart function due to the volume loading of pregnancy, which is

reversible. It is likely that cardiac function improves in women with preeclampsia postpartum.

We found no relationship between the HFA-PEFF score and maternal or fetal core outcomes, which served as a measure of disease complexity. However, core outcomes were highly prevalent, affecting over 80% of women with preeclampsia, resulting in a limited number of cases without complications. The study was likely underpowered to detect differences in this outcome because the sample size calculation was not designed for this specific endpoint. In a multivariate analysis, women with SGA infants had higher HFA-PEFF scores, indicating a possible association. However, this finding must be interpreted with caution because of the small sample size and multiple outcomes analyzed. Notably, Melchiorre *et al.* [20] reported a connection between fetal growth restriction (FGR) and diastolic

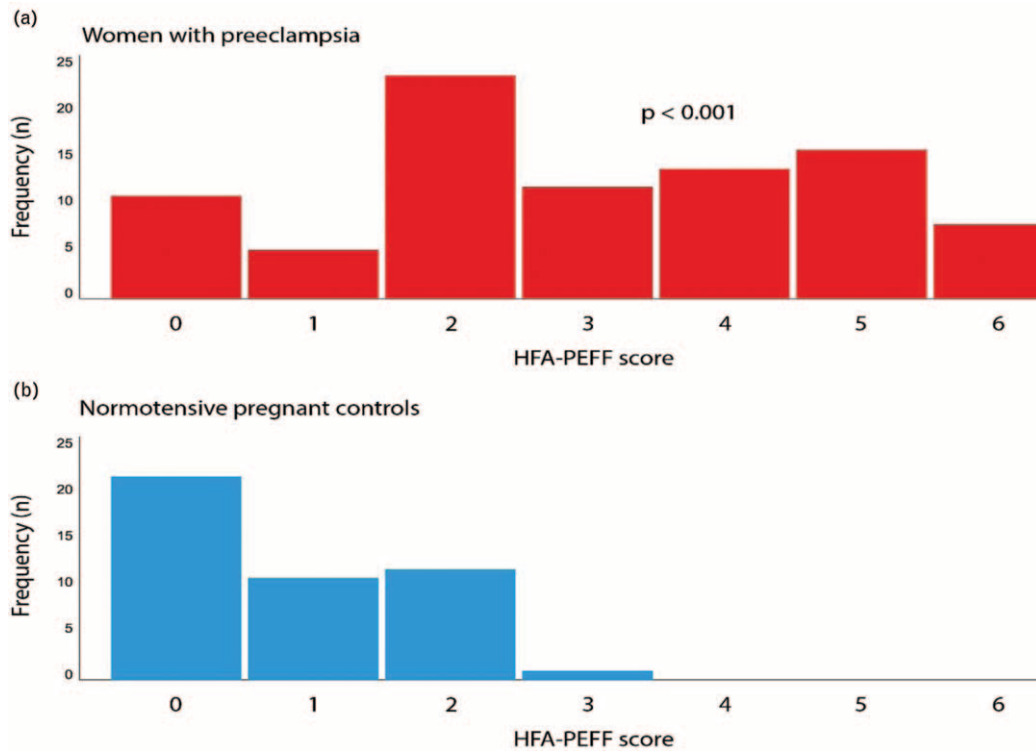


FIGURE 2 HFA-PEFF score (0–6) in patients with preeclampsia (a) and normotensive pregnant controls (b). Women with preeclampsia had a median HFA-PEFF score of 3 points (IQR 2–5), compared to a score of 1 point (IQR 0–2) in normotensive controls ($P < 0.001$, Mann–Whitney U test). HFA-PEFF, Heart Failure Association – Pretest assessment, Echocardiography and Functional testing, and Final etiology; IQR, interquartile range.

TABLE 3. Maternal age, BMI, gestational age, blood pressure, s-FLT/PIGF ratio and maternal and fetal core outcomes in relation to HFA-PEFF score (low score, intermediary score and high score) in women with preeclampsia

Category	Variable	Low score 0–1 points ($n=16$)	Intermediary score 2–4 points ($n=50$)	High score 5+ points ($n=24$)	P
Background data	Age at inclusion (years)	31 (29–33)	30 (27–34)	31 (29–36)	0.694
	BMI (kg/m^2)	27 (24–30)	25 (22–29)	25 (23–31)	0.693
	Gestational age at diagnosis (weeks+days)	33+4 (31+5–35+6)	34+5 (31+4–37+2)	32+4 (29+1–35+4)	0.510
	Gestational age at echocardiography (weeks+days)	34+4 (32+3–36+5)	35+0 (32+1–37+4)	34+3 (30+6–36+2)	0.772
Blood pressures	SBP at echocardiography (mmHg)	147 ± 12	146 ± 13	146 ± 14	0.931
	DBP at echocardiography (mmHg)	90 ± 10	91 ± 11	91 ± 9	0.948
Biomarker	sFlt/PIGF	84 (60–161)	131 (60–200)	178 (92–302)	0.036
Maternal core outcomes	Acute kidney Injury	0 (0)	4 (8)	1 (5)	0.700
	Stroke	0 (0)	0 (0)	0 (0)	–
	Pulmonary edema	0 (0)	0 (0)	1 (0)	0.147
	Liver hematoma/rupture	0 (0)	0 (0)	0 (0)	–
	Eclampsia	0 (0)	0 (0)	0 (0)	–
	Low platelets	0 (0)	3 (6)	0 (0)	0.814
	Raised liver enzymes	1 (6)	8 (15)	2 (9)	0.991
	Coma	0 (0)	0 (0)	0 (0)	–
	Retinal detachment	0 (0)	0 (0)	0 (0)	–
	Cortical blindness	0 (0)	0 (0)	0 (0)	–
	Placental abruption	0 (0)	2 (4)	0 (0)	0.848
	Postpartum hemorrhage	2 (12)	11 (21)	5 (23)	0.579
	Maternal admission to ICU	0 (0)	0 (0)	0 (0)	–
	Maternal death	0 (0)	0 (0)	0 (0)	–
Fetal core outcomes	Fetal death	0 (0)	2 (4)	0 (0)	0.848
	Admission to neonatal unit, respiratory support	10 (22)	21 (47)	14 (31)	1
	Gestational age at delivery (weeks+days)	36+2 (33+4–37+3)	35+6 (34+0–37+5)	34+5 (32+0–36+6)	0.613
	Delivery before week 37+0	11 (19)	28 (49)	18 (31)	0.396
Small-for-gestational-age infant	3 (19)	12 (24)	13 (54)	0.011	
Neonatal seizures	0 (0)	0 (0)	0 (0)	–	
Any maternal or fetal core outcomes	14 (88)	40 (80)	21 (88)	0.887	

Values are presented as n (%), median, interquartile range. Mann–Whitney U test. Jonckheere–Terpstra was used for assessing continuous data into three score groups. sFlt-1/PIGF, soluble fms-like tyrosine kinase-1/placental growth factor ratio. Maternal and fetal core outcomes: details in Supplement, <http://links.lww.com/HJH/C872>. A P value < 0.05 is considered significant.

dysfunction. We speculate that a common link between FGR and heart dysfunction in preeclampsia could be microvascular dysfunction, which is considered a key contributor to both the pathophysiology of placental dysfunction seen in preeclampsia and the development of cardiac dysfunction in other populations [10,21,22]. A high-score group was also associated with higher sFLT/PIGF ratios, which describes microvascular dysfunction and is clinically used to diagnose preeclampsia [23]. This is also in line with microvascular dysfunction possibly being a link between placental dysfunction and diastolic dysfunction in preeclampsia [24].

An association between early onset (<34 weeks) preeclampsia and more severe heart dysfunction suggested by others could not be confirmed in this study [10].

Beyond the core outcomes, we did not assess other potential outcomes that could have provided additional insights, such as respiratory rate or other symptoms of heart failure. A large proportion of the study population had high HFA-PEFF scores, which are associated with diastolic dysfunction and a high risk of HFpEF in other populations, suggesting that a proportion of women with preeclampsia experience increased LV filling pressures. This underscores the importance of intensive blood pressure control and avoiding hypervolemia, which are key principles in preeclampsia management that also help reduce cardiac stress. This could be particularly important in clinical situations, such as postpartum autotransfusion due to uterine contraction, postpartum hemorrhage requiring transfusion, induction of general anesthesia, or spinal blockade. Given these factors and that women with pulmonary edema in preeclampsia have been shown to have preserved systolic function, it is possible that pulmonary edema in preeclampsia is due to HFpEF [25–27].

The present study has several limitations that need to be taken into consideration. Inclusion pace was initially low due to limited availability of study personnel and echocardiographic competence. However, inclusion was performed consecutively on those days study resources were available.

The fact that echocardiography was only performed during office hours, may introduce an inclusion bias, as the most affected women are delivered more urgently and may be underrepresented. We only partially succeeded in matching the normotensive control group and preeclampsia group by gestational age, likely because several controls developed preeclampsia and were excluded. Despite this, there was substantial overlap in gestational age at echocardiography between the groups, and therefore probably did not affect the results. NT-proBNP levels can be influenced by obesity and kidney failure; however, the prevalence of kidney failure and BMI levels were similar in the three HFA-PEFF score groups. Therefore, we do not think that this has a major impact on NT-proBNP levels. One strength was that all women in the study were included in the national maternity care program; therefore, early diagnosis and treatment were likely, and normal blood pressure was ascertained before diagnosis.

In conclusion, the HFA-PEFF scoring system proves to be a useful tool for characterizing cardiac dysfunction in women with preeclampsia, with significantly higher scores across all three domains compared to normotensive controls. In this

study, in a high-resource setting, at least one woman out of four has a high score, indicating a greater likelihood of developing HFpEF. We propose that NT-proBNP could serve as a screening marker, as levels exceeding 125 mmol/l – after optimization of antihypertensive therapy – are necessary to reach a high score in preeclampsia. The clinical relevance and management of a high HFA-PEFF score in preeclampsia need to be further assessed in larger, adequately powered studies specifically designed to address these questions.

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Conflicts of interest

There are no conflicts of interest.

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